REMARKS

The above amendments enter no new matter. Support for the amendment to claim 1 can be found throughout the application, for example at pages 26-27 and at page 15. Support for the amendment to claim 4 can be found throughout the application, for example, at pages 26-27 and at page 15. Support for the amendment to claim 7 can be found throughout the application, for example, at page 26-27. Support for the amendment to claim 8 can be found, for example, at page 15.

The Examiner has acknowledged Applicants' intent to claim priority to GB 9621129.7. However, the Examiner notes that the oath or declaration does not acknowledge the filing of any foreign application. Accordingly, Applicants have prepared a new Oath or Declaration for signature by the inventors of the instant invention. To date the only executed Declaration received by Applicants is from inventor Ian G. Rennie. That Declaration, with the foreign priority claim, is included with this response. The remaining two Declarations will be forwarded to the Examiner as soon as possible.

OBJECTIONS

The Office Action states that the disclosure is objected to because of certain informalities. Accordingly, the indicated text on page 24 of the specification has been deleted by amendment. Furthermore, claims 7 and 8 have been objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim may not properly depend from another multiple dependent claim. Accordingly, claims 7 and 8 have been amended to depend from only "claims 4 or 5," neither of which is itself a multiple dependent claim, and analogous new claims 10, 11, and 12 which depend from the multiple dependent claims 6 and 7, have been added. Applicants believe these amendments overcome the asserted objection under 37 CFR 1.75(c).

REJECTIONS

Rejections Under 35 U.S.C. §112, first paragraph-enablement

The Office Action states that claims 4-9 have been rejected under 35 U.S.C. 112, first paragraph because the specification, does not reasonably provide enablement for methods which detect the presence of IL-1RN (VNTR) alleles as indicative of any disease other than proliferative diabetic retinopathy. In the interest of expediting proliferation, and not in

acquiescence to this rejection, Applicants have amended claim 7 as specified above to indicate that the method of the invention is directed to associations between a DNA genetic polymorphism pattern and "increased risk of sight-threatening diabetic retinopathy." This amendment obviates this rejection under 35 U.S.C. 112, first paragraph and, accordingly, Applicants respectfully request reconsideration and removal of the rejection.

The Office Action further states that "(T)he specification is not enabling for methods which detect alleles other than IL-1B (-511) allele 2, IL-1A (-889) allele 2 or IL-1RN (VNTR) allele 2 polymorphisms." In the interest of expediting proliferation, and not in acquiescence to this rejection, Applicants have amended claim 4 as specified above to indicate that the method of the invention is directed to "identifying a genetic polymorphism pattern comprising a polymorphism selected from the group consisting of: IL-1RN (VNTR) allele 2, IL-1 A (-511) allele 2, and IL-1B (-889) allele 2". This amendment obviates this rejection under 35 U.S.C. 112, first paragraph and, accordingly, Applicants respectfully request reconsideration and removal of the rejection.

Rejections Under 35 U.S.C. §112, second paragraph

The Office Action states that claims 1-9 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the invention. In the interest of expediting proliferation, and not in acquiescence to this rejection, Applicants have amended claim 1 as specified above to indicate that the method of the invention is directed to "identification of a diabetic patient's genetic polymorphism pattern at IL-1A (-889), IL-1B (-511), and IL-1RN (VNTR)." Accordingly, reconsideration and removal of the rejection is respectfully requested.

The Office Action further rejects claim 3 as indefinite for the recitation of "whether the means for determining genetic polymorphism pattern include restriction enzyme digestion." Accordingly, Applicants have amended claim 3 to indicate the kit "includes a restriction enzyme selected from the group consisting of: *Nco I*, *Ava I* and *Bsu36I*." Accordingly, reconsideration and removal of the rejection is respectfully requested.

Applicants believe the rejection of claims 5-8 as indefinite for the recitation of "control patterns" refers to the language in independent claim 4 from which claims 5-8 depend. This language has already been removed by the amendment to claim 4 discussed above. Clarification on this point is respectfully requested, however Applicants believe these amendment to claims 4 obviates this rejection and, accordingly, reconsideration and removal of the rejection is

respectfully requested. Similarly, Applicants believe amendments already made to claims 7 and 8 obviate rejections of these claims under 35 U.S.C. § 112, second paragraph.

Finally, the rejection of claim 9 under 35 U.S.C. § 112, second paragraph for the recitation of "multiple genetic polymorphism" is respectfully traversed because the specification provides specific guidance of multiple polymorphic patterns (e.g. comprising at least three copies of allele 2 at the Il-1A (-889) locus and IL-1B (-511 locus) (see page 27) or zero copies of allele 2 at the IL-1 RN (VNTR) (see page 15)). Accordingly, reconsideration and removal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. §103

The Office Action states that claims 1 and 2 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Mansfield (Gastroenterology (1994) 106: 637-42). In particular, the Office action states that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have packaged the primers and DNA collection means required to practice the method of Mansfield into a kit. In the interest of expediting prosecution and not in acquiescence to the Examiner's rejection, Applicants have amended claim 2 so as to delete certain oligonucleotide primers (i.e. SEQ ID Nos. 1, 3, 4, 5, 6 and 8) which the Office Action states were disclosed by the Mansfield et al. reference for use in another application. Applicants believe this amendment obviates the rejection of claim 3 under 35 U.S.C. § 103(a) in view of Mansfield et al. and, accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Still further, Applicants traverse the rejection of claim 1 in view of the Mansfield et al. reference for the reasons which follow. First, there is no motivation to combine the teachings of Mansfield et al., directed to detecting polymorphisms associated with ulcerative colitis, with what is asserted to be "conventional" knowledge in the field of "reagent kits for performing DNA detection assays." In particular, the Office Action does not cite a "conventional" polymorphism-determining kit which would be well known in the art and which a skilled artisan working at the time of the invention might modify to produce the instant kit for identifying a diabetic patient's genetic polymorphism pattern at IL-1RN. While other kits useful for, e.g., cloning and expression operations by scientists may have existed at the time of the invention, the instant kit is directed uniquely to a diagnostic field of use for diabetic retinopathy patients being treated in a medical setting. Still further, the skilled artisan would not have been motivated to combine any such kit, if it did exist, with the teachings of Mansfield et al. to arrive at the instant kit because the teachings of Mansfield et al. deals with ulcerative colitis and not diabetic

retinopathy. Applicants therefore assert that the kit claimed in instant claim 1 is not *prima facie* obvious in view of the cited reference and, accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

The Office Action further states that claim 3 has been rejected under 35 U.S.C. § 103(a) in view of Mansfield et al. (cited above) and further in view of Kornman (U.S. Patent No. 5,686,246). Applicants respectfully traverse this rejection for the reasons which follow. First, there is no motivation to combine the Mansfield et al. reference with the Kornman et al. reference to arrive at the instant claimed invention. In particular, Mansfield et al. deals with polymorphisms which predispose to ulcerative colitis and Kornman et al. deals with polymorphisms which predispose to periodontal disease. Accordingly, the skilled artisan working at the time of the instant invention would have had no motivation to combine the teachings from these two sources to arrive at the instant claimed invention directed to diagnostic kits for identifying a diabetic patient's genetic polymorphism pattern at IL-1RN. Accordingly, the kit claimed in amended claim 3, as presented above, is not *prima facie* obvious in view of the cited references.

Furthermore Applicants note that, notwithstanding the fact that the Kornman et al. patent may be available under 35 U.S.C. §102(e), the American Inventors Protection Act of 1999 (officially cited as Pub. L. No. 106-113) provides for amendment of 35 U.S.C. § 103(c) to preclude application of subject matter which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. Applicants note that, at the time the instant invention was made, the subject matter described in the Kornman et al. patent and the instant claimed invention were "owned by the same person or subject to an obligation of assignment to the same person" (i.e. Interleukin Genetics which was previously known as Medical Science Systems). Applicants note that this new provision of 35 U.S.C. § 103(c) applies only to those patent applications filed on or after November 29, 1999. Accordingly, a procedural technicality precludes the application of the substantive law provided by the new provisions of 35 U.S.C. § 103(c), which would otherwise remove this reference as prior art against the instant claimed invention in an obviousness rejection. Applicants respectfully reserve the right to remove the Kornman et al. reference under 35 U.S.C. § 103(c) by filing a continuing application in this case. Nevertheless, as discussed above, Applicants believe this procedural mechanism is not needed because the Kornman et al reference in view of the Mansfield et al. reference does not render the claimed

invention *prima facie* obvious as discussed above. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. If for any reason a telephonic conference with the Applicant would be helpful in expediting prosecution of the instant application, the Examiner is invited to call Applicants' Agent at (617) 832-1764. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited.

If there are any other fees due in connection with the filing of this Response, please charge the fees to our Deposit Account No. 06-1448.

Respectfully submitted,
FOLEY, HOAG, & ELIOT

April 11, 2001

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SPECIFICATION

(marked-up version of replacement paragraphs of the specification showing changes made.

On page 1, immediately following the title, the first full paragraph, inserted previously by Applicant's Preliminary Amendment filed on March 10, 1998, was amended as follows:

This application is [based on copending] the national phase of PCT Patent Application GB97/02790 filed on October 9, 1997; which [was based on] claims priority to UK Provisional Application No. GB 9621129.7, filed on October 10, 1996.

On page 24, the third full paragraph beginning at line 10 was amended as follows:

[[There was text missing here in the original UK filing] with] 1.75mM (final concentration) $MgCl_2$ and cycling protocol of 1 cycle at 96° C for 1 minute;

30 cycles of [94° C (1 minute), 60° C (1 minute), 70° C (1 minute)]; and

1 cycle at 70° C for 2 minutes.

CLAIMS

1. **(Once Amended)** A kit for the identification of a diabetic patient's genetic polymorphism pattern at IL-1A (-889), IL-1B (-511), and IL-1RN (VNTR) associated with increased risk of sight-threatening retinopathy, said kit comprising:

(a) DNA sample collecting means, and

(b) means for determining a genetic polymorphism pattern for IL-1A (-889), IL-1B (-511), and IL-1RN (VNTR).

2. **(Once Amended)** A kit according to claim 1, wherein the means for determining genetic polymorphism pattern comprises at least one polymerase chain reaction (PCR) primer wherein the PCR primer is selected from:

[5'AAG CTT GTT CTA CCA CCT GAA CTA GGC 3' (SEQ ID NO: 1);]
5'GTA CCT TCC GAG TAT ACA TT 3' (SEQ ID NO: 2);
[5'TGG CAT TGA TCT GGT TCA TC 3' (SEQ ID NO: 3);
5'GTT TAG GAA TCT TCC CAC TT 3' (SEQ ID NO: 4);
5'CTCAGCAACACTCCTAT 3' (SEQ ID NO: 5);
5'TCCTGGTCTGCAGGTAA 3' (SEQ ID NO: 6);]
5'TGTTCTACCACCTGAACTAGGC 3' (SEQ ID NO: 7);
[5'TTACATATGAGCCTTCCATG 3' (SEQ ID NO: 8);]
5'AAGCTTGTTCTACCACCTGAACTAGGC 3' (SEQ ID NO: 9); and
5'TTACATATGAGCCTTCCATG 3' (SEQ ID NO: 10).

3. **(Once Amended)** A kit according to claim 1 or 2, wherein the means for determining the genetic polymorphism pattern [include] includes a restriction enzyme [digestion with restriction enzymes] selected from the group consisting of: *NcoI, AvaI,* and *Bsu35I.*

4. **(Once Amended)** A method of predicting increased risk of sight-threatening diabetic retinopathy, comprising [the steps of:

(a)] identifying in isolated genomic DNA from a sample previously taken from a diabetic patient a genetic polymorphism pattern [for the genes IL-1A, IL-1B and IL-1RN] comprising a polymorphism selected from the group consisting of: IL-1RN (VNTR) allele 1, IL-1 A (-511) allele 2, and IL-1B (-889) allele 2[;]

[(b) comparing the identified pattern to control patterns of known polymorphisms; and

(c) identifying diabetic patients expressing a genetic polymorphism pattern associated with increased risk of sight-threatening diabetic retinopathy] , wherein the presence of the genetic polymorphism pattern is predictive of an increased risk of sight-threatening diabetic retinopathy.

5. A method according to claim 4, wherein said step for identifying in the DNA a genetic polymorphism pattern for IL-1A, IL-1B and IL-1RN comprises amplification of target DNA sequences with a polymerase chain reaction (PCR) and at least one PCR primer, wherein the PCR primer is selected from the group consisting of:

5'AAG CTT GTT CTA CCA CCT GAA CTA GGC 3' (SEQ ID NO: 1);
5'GTA CCT TCC GAG TAT ACA TT 3' (SEQ ID NO: 2);
5'TGG CAT TGA TCT GGT TCA TC 3' (SEQ ID NO: 3);
5'GTT TAG GAA TCT TCC CAC TT 3' (SEQ ID NO: 4);
5'CTCAGCAACACTCCTAT 3' (SEQ ID NO: 5);
5'TCCTGGTCTGCAGGTAA 3' (SEQ ID NO: 6);
5'TGTTCTACCACCTGAACTAGGC 3' (SEQ ID NO: 7);
5'TTACATATGAGCCTTCCATG 3' (SEQ ID NO: 8);
5'AAGCTTGTTCTACCACCTGAACTAGGC 3' (SEQ ID NO: 9); and
5'TTACATATGAGCCTTCCATG 3' (SEQ ID NO. 10).

6. A method according to claim 4 or 5, wherein said step for identifying in the DNA a genetic polymorphism pattern for genes IL-1A, IL-1B and IL-1RN comprises restriction enzyme digestion with restriction enzymes *NcoI, AvaI,* and *Bsu36I.*

7. **(Once Amended)** A method according to [any of claims] claim 4 or 5 [to 6], wherein the DNA genetic polymorphism pattern associated with increased risk of [clinically-significant macular edema] sight-threatening diabetic retinopathy comprises the presence at the combined loci of IL-1A plus IL-1B of at least three copies of the rarer allele for each loci (allele 2) between the two loci.

8. **(Once Amended)** A method according to claim 4 or 5, wherein the DNA genetic polymorphism pattern predicting increased risk of diabetic retinopathy does not include the IL-1RN 2,2 pattern associated with decreased risk of proliferative diabetic retinopathy [comprises the presence of the genotype IL-1RN 2,2].

9. A method for predicting risk of sight-threatening diabetic retinopathy, comprising the steps of:

(a) identifying in isolated genomic DNA from a sample previously obtained from a diabetic patient a genetic polymorphism pattern for genes IL-1A, IL-1B and IL-1RN;

(b) identifying in the DNA a genetic polymorphism pattern for other genes associated with sight-threatening diabetic retinopathy;

(c) determining the number of polymorphisms carried by the diabetic patient that are associated with sight-threatening diabetic retinopathy risk, and identifying diabetic patients expressing a multiple genetic polymorphism pattern associated with risk of sight-threatening diabetic retinopathy.

10. **(Once Amended)** A method according to claim 6, wherein the DNA genetic polymorphism pattern associated with increased risk of [clinically-significant macular edema] sight-threatening diabetic retinopathy comprises the presence at the combined loci of IL-1A plus IL-1B of at least three copies of the rarer allele for each loci (allele 2) between the two loci.

11. A method according to claim 6, wherein the DNA genetic polymorphism pattern associated with decreased risk of proliferative diabetic retinopathy comprises the presence of the genotype IL-1RN 2,2.

12. A method according to claim 7, wherein the DNA genetic polymorphism pattern associated with decreased risk of proliferative diabetic retinopathy comprises the presence of the genotype IL-1RN 2,2.